

REMARKS

Status of the Claims

Claims 39-50, 52-70, 81, 82 and 84-92 were pending. Claims 46-47, 50, 53, 54, 59, 70, 86-88, are canceled herein without prejudice or disclaimer. Claims 39-45, 48, 49, 52, 55-58, 60-69, 81, 82, 84, 85 and 89-92 are presently pending.

Claims 39-45, 48, 49, 55-58, 61, 62, 65, 81, 82 and 85 are amended herein. Applicants submit that no new matter is added by amendment.

Claim Amendment Support

Claim 39 is amended to recite a membrane module comprising at least one tube-shaped dialysis membrane, wherein dialysis fluid is circulated through the module outside of the tube-shaped membrane and culture fluid containing cells is circulated through the inside of the tube-shaped membrane, the membrane separating the culture fluid from the dialysis fluid in the module, a first gas is introduced into the culture fluid in the culture vessel and a second gas is introduced into the culture fluid in the tube-shaped dialysis membrane. Support for the amendment may be found in FIG. 3 and the Specification at least at pg. 5, lines 34-35; pg. 6, lines 5-9; and pg. 12, lines 20-36. The Specification at pg.17, line 9 to pg. 18, line 28 discusses the embodiment illustrated in FIG. 3, in which the "dialysis membrane in the membrane module 8 forms tubes, summarily denoted tube-shaped membrane herein, through which the culture fluid is led. The dialysis fluid flows through the spaces located in between and separated from the culture fluid by the membrane material." "In the case of a suspension culture in culture space 2, the cells here flow through the interior of the tube-shaped membrane(s) from bottom to top. The dialysis fluid which is exchanged with the container for dialysis fluid 1 via the lines 11 and 12 flows around the outer wall of the membrane."

Support for the amendment to claim 40 is supported by FIG. 3 and the Specification at least at pg. 6, lines 8-9 and 15 which recite that, "an outlet of the gas supplying means is located in at least one of the spaces formed by the tube-shaped membrane," and "the gas supplying means is a tube," and also at pg. 12, lines 20-27. At pg. 18, lines 16-17 the Specification states that, "The gas is introduced with a certain excess pressure via the tubes 16 into the internal space of the membrane 3."

Support for the amendments to claims 41 and 42 is found in the Specification at least at pg. 3, lines 34-38, which discloses, in an alternative embodiment, introducing the second gas into the dialysis fluid in the container for dialysis fluid, the gas transferred from the dialysis fluid to the culture fluid in the membrane module via the dialysis membrane. The amendment to claim 41 is further supported in the Specification at pg. 10, lines 17-22, which discusses transport via the membrane by diffusion.

Support for the amendment to claim 43 may be found in the Specification at least at pg. 4, lines 1-2, which discloses introducing the second gas by both the direct method (of claim 40) and the indirect method (of claims 41 and 42).

Support for the amendments to claims 44 and 45 is supported by the Specification at least at pg. 6, lines 1-3, which recites, "the diameter of the space formed by the tube-shaped membrane to be about 3-10, preferably 6-8 mm."

Support for the amendment to claim 48 is supported by the Specification at least at pg. 6, lines 23-24, which recites that, "the outlet of the gas supplying means is shaped like a nozzle."

Support for the amendment to claim 49 is supported by the Specification at least at pg. 4, lines 18-20, which discusses the composition of the membrane of the membrane module to be composed of material selected from the group comprising regenerated cellulose, polyamide, polypropylene and polysulfone. To conform with standard Markush group language, "comprising" is replaced with "consisting of."

Support for the amendments to claims 55-57 may be found in the Specification at least at pg. 4, line 32 to pg. 5, line 1.

Support for the amendment to claim 58 may be found in the Specification at least at pg. 5, lines 3-4

Support for the amendments to claims 61 and 62 may be found in the Specification at least at pg. 5, lines 13-15.

Claim 65 is also amended to conform more closely to the standard Markush language.

Claims 81, 82 and 85 are amended to conform to embodiments illustrated by FIG. 4, as discussed by the Specification at pg. 13, lines 13-30. As stated, flat membranes are arranged with, “two membranes forming a space through which the culture fluid 17 flows. The dialysate 18 flows through the external part.” In certain embodiments, “[t]he membranes are supported by a supporting structure 19.” The embodiment is further supported in the Specification at pg. 18, line 36 to pg. 19, line 30. The element of introducing first and second gases into different spaces is supported in the Specification at least at pg. 3, lines 9-17.

Rejection of Claims Under 35 U.S.C. §112, 1st Paragraph, Written Description

Rejection of claim 70 under 35 U.S.C. §112, first paragraph for lack of written description is mooted by the cancellation of the claim.

Rejection of Claims Under 35 U.S.C. 112, 2nd Paragraph

Rejection of claim 70 under 35 U.S.C. §112, 2nd paragraph is mooted by the cancellation of the claim.

Applicants respectfully submit that the metes and bounds of amended claim 45 would be clear to the skilled artisan, as the element that was the subject of the 112, 2nd paragraph rejection has been removed from amended claim 45.

Rejection of Claims Under 35 USC 103

Claims 39-50, 52-70, 81, 82 and 84-92 were rejected under 35 U.S.C. §103(a) as obvious over Portner et al.

A *prima facie* case of obviousness requires: (1) a teaching or suggestion of all of the claim limitations; (2) a suggestion or motivation to modify or combine the teachings of the applied prior art; and (3) a reasonable expectation of success in reaching the claimed invention. (MPEP § 2142)

Applicants respectfully submit that, as applied to the amended claims, all three requirements of a *prima facie* case of obviousness are lacking. First, Applicants note that claim 39 is amended to recite a method of use of a reaction system comprising a membrane module with at least one tube-shaped dialysis membrane, wherein dialysis fluid is circulated through the membrane module

outside of the tube-shaped dialysis membrane and culture fluid containing cells is circulated through the membrane module inside of the tube-shaped dialysis membrane. Amended claim 39 further recites introducing a second gas into the culture fluid within the at least one tube-shaped dialysis membrane. Applicants submit that these elements are nowhere disclosed in the cited reference of Portner et al.

The Action refers to Fig. 3 of Portner as disclosing a large diameter tubular dialysis membrane. Applicants note that the system illustrated in Fig. 3 of Portner is a single vessel system, in which the membrane surrounds the entire compartment of the culture chamber. This is quite distinct from the claimed 3-component system, with separate dialysis container, culture vessel and membrane module. Instant claim 39 recites a membrane module comprising at least one tube-shaped dialysis membrane, not a dialysis membrane surrounding a culture chamber in a single vessel system. The element of a membrane module comprising at least one tube-shaped dialysis membrane is nowhere disclosed in the Portner reference.

Applicants further submit that no suggestion or motivation is provided in the cited prior art to modify the prior art disclosures to include the elements of use of a reaction system comprising a membrane module with at least one tube-shaped dialysis membrane, wherein dialysis fluid is circulated through the membrane module outside of the tube-shaped dialysis membrane and culture fluid containing cells is circulated through the membrane module inside of the tube-shaped dialysis membrane or introducing a second gas into the culture fluid within the at least one tube-shaped dialysis membrane. No motivation is provided in Portner to make the claimed combination and in fact Portner teaches away from the use of a two-vessel system with separate dialysis module. Rather than motivating the skilled artisan to combine one or more tube-shaped dialysis membranes in a separate membrane module with a two-vessel system, Portner clearly leads the skilled artisan to consider the use of a single-vessel dialysis reactor. Portner states at pg. 404, col. 2, 4th and 5th paragraphs that,

The two-vessel arrangement has some disadvantages. Sterilization of this complex system might be a problem. As the fermentation broth has to be pumped through the external module, suspended cells (Fig. 2a) are exposed to mechanical stress during this pumping procedure and can suffer from oxygen limitation. Furthermore it has turned out to be a quite sophisticated control problem to balance the liquid levels in both tanks, at least in

laboratory-scale systems. As an alternative, single-vessel dialysis reactors were proposed for the laboratory scale.

Thus, the skilled artisan reading Portner would be led to believe that the difficulties of a two-vessel system may be resolved by using instead a single-vessel system. Since the single vessel system eliminated certain problems with the two-vessel system, such as mechanical stress from pumping and oxygen limitation in the membrane module, Portner provided no motivation or suggestion to modify a two-vessel system to include one or more tubular dialysis membranes or to introduce a second gas into the culture fluid in a membrane module.

Applicants further submit that the skilled artisan could have had no reasonable expectation of success in making and using the claimed invention, since Portner would have led the skilled artisan to believe that the claimed 3-component system would still pose difficulties with mechanical stress to the cells during the pumping of culture fluid through the module, with sterilization problems and with the “quite sophisticated control problem to balance the liquid levels in both tanks.”

Since the cited prior art reference of Portner (1) is missing the element of claim 39 of a membrane module comprising a tubular dialysis membrane; (2) provides no motivation or suggestion to modify a two-vessel system as claimed; (3) provides no reasonable expectation of success in achieving the claimed invention, Applicants submit that a prima facie case of obviousness has not been established for amended claims 39-45, 48, 49, 52, 55-58 and 60-69. Reconsideration and withdrawal of the rejection are respectfully requested.

Applicants further submit that the reaction system of claim 82 and the method of use of a reaction system of claim 81, incorporating a membrane module as illustrated in FIG. 4, are also not obvious over the cited prior art. As discussed in the Specification at pg. 18, line 36 to pg. 19, line 17, the membrane module illustrated in FIG. 4 had previously been known only within the context of hemodialysis, not cell culture, and it was surprising that such a hemodialysis membrane module would be of use in the context of cell culture. The Office Action points to no prior art of record disclosing the use of a membrane module according to FIG. 4, in a reaction system or method of use for cell culture. Further, there was no suggestion or motivation in the prior art of record to adapt the

membrane module of FIG. 4 for use in cell culture, and therefore no reasonable expectation of success that the membrane module of FIG. 4 could be used for cell culture.

Conclusion

For the reasons stated above, Applicants submit that the amended claims are in condition for allowance and requests withdrawal of the rejections.

Respectfully submitted,



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